

INTRODUCTION

A perspective on liposomal amphotericin B (AmBisome®)

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Despite considerable progress in the past few years, the rates of morbidity and mortality due to invasive fungal infections are still unacceptably high. There is a need for antifungal drugs with new mechanisms of action that have a broad spectrum of activity (including resistant pathogens) and can be administered both intravenously and orally. Moreover, agents with these characteristics plus a favourable safety profile and few drug interactions would be attractive to evaluate as components of combination therapy regimens for infections that are difficult to treat.

Predicting the clinical outcome of a systemic mycosis is often a difficult task, especially when microbiological resistance is one of the factors contributing to therapeutic failure. Some of these factors are host-related, e.g. immune state, site and severity of infection, and poor compliance with therapy, while others are associated with the drug's characteristics, e.g. dosage, type of compound (fungistatic/fungicidal), pharmacokinetic properties, and drug–drug interactions.

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MR has acted as a paid consultant to Gilead Sciences (Europe) Ltd and is a member of the Schering-Plough Inc. and MSD Inc. speakers bureaux. BdP is a member of the Gilead Sciences (Europe) Ltd, Merck & Co. Inc. and Pfizer Inc. speakers' bureaux. Third guest editor: MCA received research funding from Pfizer in 2007 (Project on PCR detection of invasive fungal infections) and has participated in Advisory Board meetings in 2007 for MSD, Schering-Plough and Pfizer. Lectures during 2007–2008 included those sponsored by Pfizer, Swedish Orphan, Cephalan, MSD and Astellas.

AMBISOME COMES OF AGE

Coming of age is the transition from adolescence to adulthood. The age at which this transition takes place varies, as does the nature of the transition. While amphotericin B deoxycholate has been considered by many to be the reference standard for the treatment of numerous invasive fungal infections for over 45 years, toxicities associated with its use often necessitate treatment modifications or discontinuation. Lipid-based formulations, including liposomal amphotericin B, were developed to decrease many of these toxicities. These agents have proven their value in a variety of clinical settings. The concept of liposomal amphotericin B was formulated in the mid-1980s, and the first treatment in the Nordic region took place in 1989. So far, over 500 000 patients have been treated with AmBisome. The use of liposomal amphotericin B continues to accelerate. Recent treatment guidelines include its use as primary therapy in certain defined situations where voriconazole is not appropriate [1]. The evidence would support the use of liposomal amphotericin B in a wide variety of clinical settings, and recent data support the ability to escalate the dose in treatment of very serious infections.

Because few comparative studies have been performed, open-label studies represent a major source of data on the efficacy of liposomal amphotericin B in proven invasive fungal infections. In addition, case reports have contributed to our knowledge regarding this antifungal agent—these are situations where all the real-life problems of diagnosis and optimal treatment are presented.

NEW MONOTHERAPY STRATEGIES

The broad spectrum and fungicidal mode of action of liposomal amphotericin B have

prompted new strategies to improve antifungal treatment beyond our current understanding and experience of empirical and pre-emptive treatment. One approach has been to assess higher dosing of liposomal amphotericin B. Indeed, the pharmacodynamic properties, preclinical data from animal models and the response rates of patients who received doses >3 mg/kg/day suggested that liposomal amphotericin B could improve outcomes and survival. However, a randomised comparative trial (AmBiLoad trial) did not demonstrate a greater benefit of a 10 mg/kg/day dose over the lower doses [2]. What is not clear is whether higher doses of liposomal amphotericin B would benefit truly high-risk patients, e.g., those with disseminated disease or zygomycosis. In the setting of invasive aspergillosis, it is clear that new strategies are needed. Recent experiences indicate that the candins used as monotherapy are not optimal and do not offer any additional benefit over other broad-spectrum agents for preventing breakthrough invasive aspergillosis for either prophylaxis or empirical usage [3–5], or as a recent European Organisation for Research and Treatment of Cancer (EORTC) study indicates, as first-line treatment for invasive aspergillosis [6]. These studies emphasise further the importance of a fungicidal agent for this disease. Moreover, new experience should be obtained with candins at higher dosages, or in combination with liposomal amphotericin B or extended-spectrum azoles.

COMBINATION STRATEGIES

The benefits of drug combinations have been demonstrated largely in infectious diseases such as human immunodeficiency virus infection and tuberculosis. Generally, the principle of combination therapy is to combine drugs with differing pharmacological targets. It has been predicted that the simultaneous inhibition of fungal cell-wall biosynthesis and disruption of cell-wall integrity may result in synergistic interactions against pathogenic yeasts and filamentous fungi.

During the past decade, new antifungals have been developed that give the clinician an opportunity to choose from a broader arsenal of drugs for the treatment of invasive fungal infections. Moreover, there is now a greater possibility of

combining agents with different modes of action to achieve an additive or synergistic action for the most severely ill patients. Clinical studies are difficult to interpret with this group of patients, since many of the small number of trials have been salvage studies, which invariably include many terminally ill patients, and there are insufficient and somewhat conflicting data from in-vitro studies, animal models and clinical reports on the relative efficacies of different antifungal combinations. Clearly, before combining agents, it is important to understand the mode of action of individual compounds. The optimal combination would possibly involve drugs with different pharmacokinetics and sites of action. Clinical studies are difficult to interpret with this group of patients, since many of the small number of trials have been salvage studies, which invariably include many terminally ill patients, and there are insufficient and somewhat conflicting data from in vitro studies, animal models and clinical reports on the relative efficiencies of different antifungal combinations. Clearly, before combining agents, it is important to understand the model of action of individual compounds. The optimal combination would possibly involve drugs with different pharmacokinetics and sites of action. Furthermore, it is important to at least rule out antagonistic effects that could be deleterious to patients.

Although using combinations of agents with different mechanisms of action is appealing, the available data are difficult to interpret. Unanswered questions include which combination would be optimal, what endpoint is appropriate, how much benefit would have to be seen to justify the adoption of combination therapy, and which populations are likely to benefit. Despite the frequent clinical use of antifungal combination therapy for primary or salvage therapy of invasive fungal infection in many centres, to date, no randomised study comparing monotherapy with combination therapy has been performed. Single-drug therapy, either as first-line or salvage treatment, rarely gives response rates $>50\%$ to 60% . Combination therapy is an attractive concept for treating invasive mycoses. Optimal combination regimens remain unclear. However, given its broad spectrum, encompassing difficult-to-treat patients, it is believed that liposomal amphotericin B is a good drug for invasive mycosis combination therapy.

A LOOK INTO THE FUTURE

Recent studies in experimental models of invasive aspergillosis have suggested that the association between amphotericin B and caspofungin decreases tissue infection and increases survival [7,8]. Case reports and retrospective studies have indicated that the combination of caspofungin with a lipid formulation of amphotericin B or an azole may be beneficial as salvage therapy. More clinical studies are obviously needed, but the following study (the Combistat trial) may serve as a model for future trials [9]. Patients with proven or probable invasive aspergillosis were randomised in a prospective, open pilot study to receive either a combination of liposomal amphotericin B at 3 mg/kg daily and caspofungin 70 mg on day 1 followed by 50 mg daily thereafter, or monotherapy with high-dose liposomal amphotericin B (10 mg/kg/day). Thirty patients (21 men and nine women) with haematological malignancies were analysed, and there were 15 patients in each arm. The median duration of treatment was 18 days for the combination group and 17 days for the high-dose monotherapy group. At the end of treatment, there were significantly more favourable overall responses (partial or complete responses; p 0.028) in the combination group (ten of 15 patients; 67%) than in the high-dose monotherapy group (four of 15 patients; 27%). Survival rates at 12 weeks after inclusion were 100% and 80%, respectively. Infusion-related reactions occurred in three patients in the high-dose monotherapy group. A two-fold increase in serum creatinine occurred in four of 17 patients (23%) who received high-dose monotherapy and one of 15 patients (7%) who received combination therapy; hypokalaemia <3 mmol/L occurred in three patients and two patients, respectively.

In addressing future trends in treatment of systemic fungal infections, it is tempting to include molecular-genetic-based diagnostics and therapeutics, and the beginning of a third age of antifungal agents. However, it is important to remind ourselves that the foundation of major advances in our understanding of systemic fungal infections has been, and will remain, careful clinical observation and the use of appropriate diagnostic tests. Most modern trends in diagnosis have resulted from strategies based on key clinical observations from the past. Disappoint-

ingly, considering that the initial reports on fungal antigen detection were published 35 years ago, the evolution of reliable tests for the definitive diagnosis of invasive fungal infections has been very slow. Further development of surrogate markers of invasive aspergillosis and systemic candidosis is urgently required. This requires considerable investment of resources. Currently, non-culture-based approaches to diagnosis have limited usefulness, with validation still being needed, although the promise of improved diagnosis of invasive aspergillosis by galactomannan detection, PCR and high-resolution computed tomography is noted.

CONCLUSION

This supplement of *Clinical Microbiology and Infection*, focusing primarily on yeast and mould infections in profoundly immunocompromised patients, reinforces the value of liposomal amphotericin B as monotherapy, or in combination with an echinocandin. The success of these strategies increasingly depends on early diagnosis. Several infection themes and diagnostic approaches are presented from all corners of the globe, indicating the diverse epidemiology of invasive fungal disease in different climatic areas and in diverse patient groups. The use of liposomal amphotericin B has been established in a wide variety of clinical settings, it has the broadest spectrum of activity of all currently used antifungals, and furthermore, resistance has only rarely been demonstrated. There is an extensive body of knowledge and history of use (familiarity with) regarding liposomal amphotericin B which has been published in the scientific and clinical literature since 1990. The number of publications implies a significant and successful level of use.

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